Writing a Protocol

Workshop Series for Clinical Research Professionals

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Outline for today

Today's Agenda

Activity

Trial Basics

Developing a research question

Activity

Protocol Details

Informed Consent

Activity

Resources at each institution

Overview of protocol

What is a protocol?
Document that details the study rationale, proposed methods, organization and ethical considerations

Purpose:
- For trial investigators and staff use protocols- to **document plans for study conduct** at all stages from participant recruitment to results dissemination
- For funding agencies, IRBs, regulatory agencies, and other groups- to **appraise the conduct and reporting** of clinical trials.

General considerations:
- Consider local requirements for multi-site/global studies
- Consider resources and processes at sites for multi-site/global studies
  eg: equipment available, supplies etc.

What does it take to write a good study protocol?

5 minutes

Huddle into groups of 3 – 4 and introduce yourself briefly

Activity 1

- What's missing?

Introduction	Participants	Data	Monitoring	Ethics
		Data collection methods	Data monitoring	
Objectives	Interventions	Data management		Confidentiality
Trial Design	Participant timeline	Outcomes (1° and 2°)		Access to data
Study setting	Sample size			Ancillary and post-trial care
	Recruitment		Auditing	
	Randomization	Interim analysis		Publication policy
	Blinding			

What does it take to write a good study protocol?

5 minutes

Answer

Introduction

- Background and rationale
- Objectives
- Trial Design
- Study setting

Participants

- Inclusion criteria
- Interventions
- Participant timeline
- Sample size
- Recruitment
- Randomization
- Blinding

Data

- Data collection methods
- Data management
- Outcomes (1º and 2º)
- Statistical methods
- Interim analysis

Monitoring

- Data monitoring
- Harms/Adverse events
- Auditing

Ethics

- Consent and assent
- Confidentiality
- Access to data
- Ancillary and post-trial care
- Publication policy

Types of trials

Meta-Analysis

Systematic Review

Randomized Controlled Trial

Cohort Study (Prospective Observational Study)

Case-control Study

Cross-sectional study

Case Reports and Series

Note: Not all types of trials require all components of the protocol

Developing a good research question

A clinical study involves research using human volunteers that is intended to **add to medical knowledge.**

Interest: Want to know more about hand-washing technique in children

What is a research question that addresses all 4 points?

Developing a good research question

Interest: Want to know more about hygiene practices in children

Question: How long do children wash their hands when asked to do so at the end of a regularly scheduled well-check appointment?

Defined start and stop time for hand-washing

Prior research establishes that hand washing time relates to overall hygiene

Study staff will…
- Consent parent/child at well-check appointment
- Ask caregiver to record time with provided stopwatch
- Only ask for one recording

Focusing on hand-washing practice in children

Developing your own research questions!

5 minutes

Activity 2

- As a group, pick a research study that you are working on
- Develop a research question
- List qualities of the question that fit in each category below

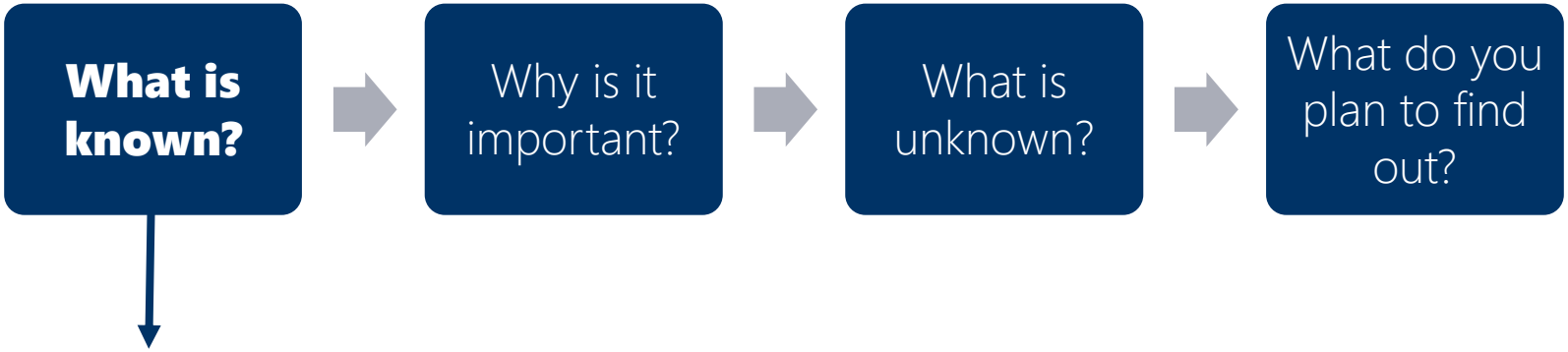
Developing your own research questions!

5 minutes

Let's hear from one group at each institution

The intro bits

Background and Objective

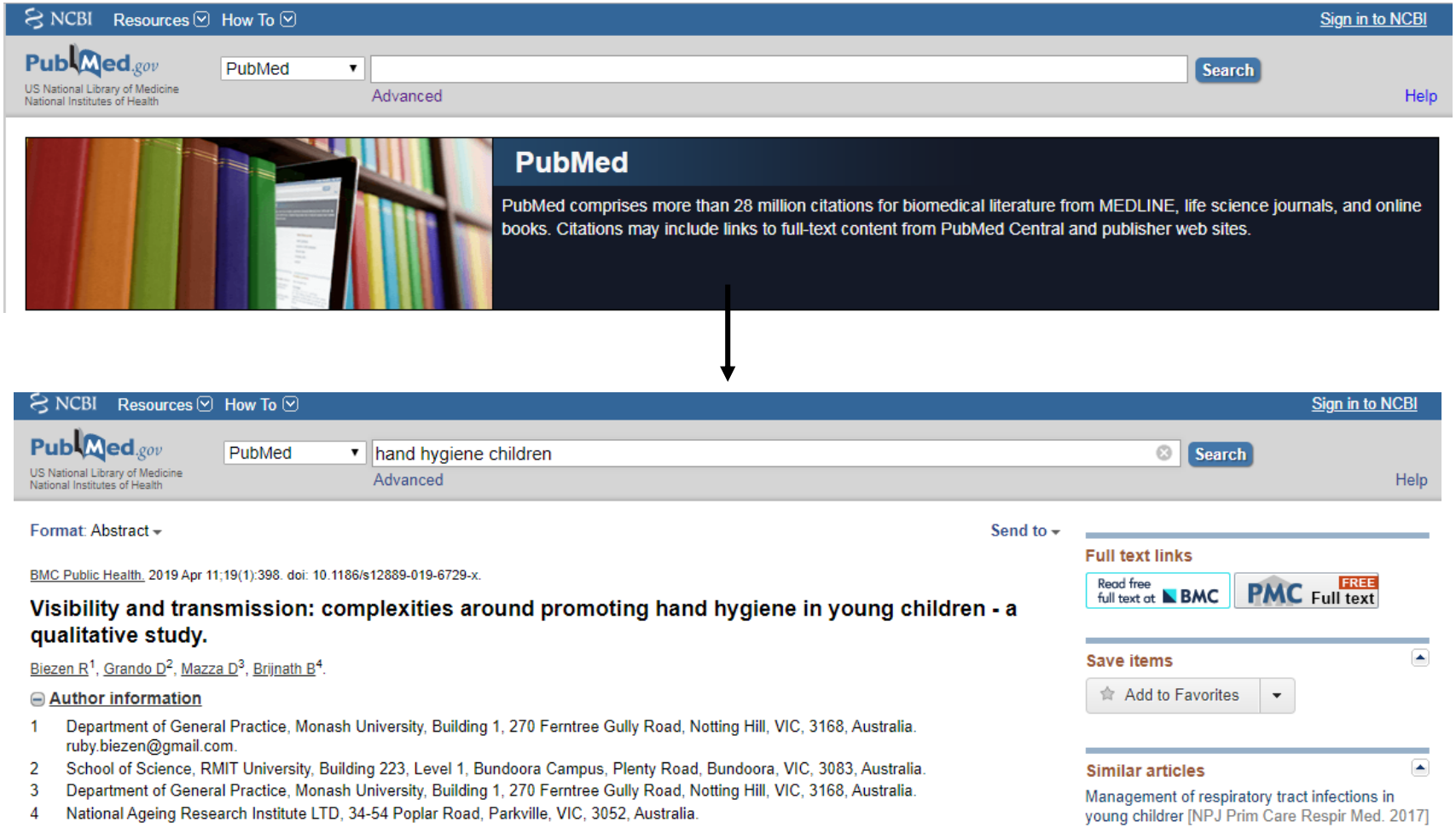


Literature search *with* references

PubMed

The intro bits

Finding medical literature



The intro bits

zotero

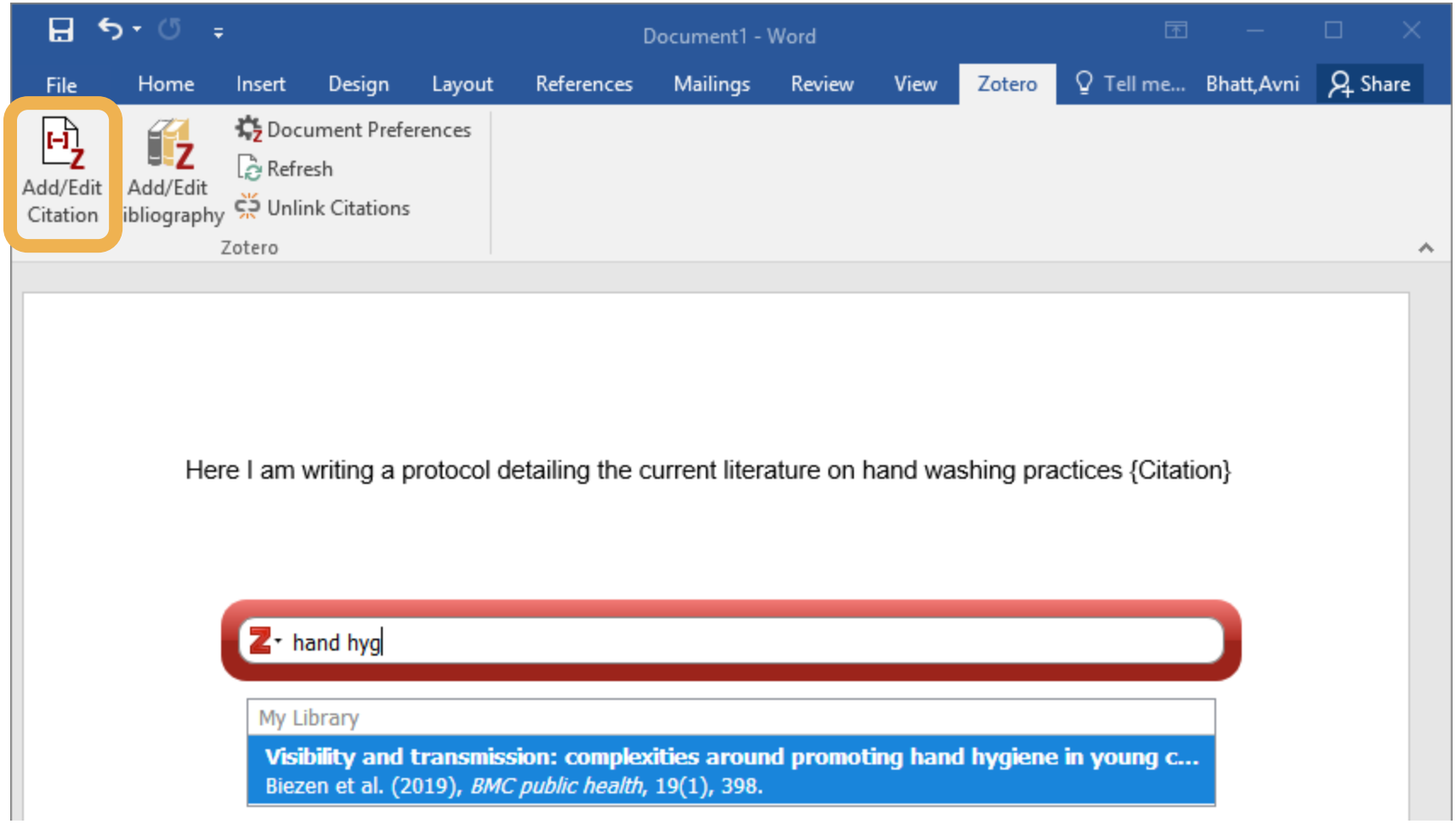
Using a citation manager

EndNote X9

Zotero Connector

The intro bits

Using a citation manager



The intro bits

Writing a strong objective statement

What is known? → Why is it important? → What is unknown? → **What do you plan to find out?**

Use action words!

Knowledge: describe, identify, examine
Relationship: associate, differentiate, relate
Create: formulate, prepare, generalize, design
Evaluate: assess, measure, support, compare

Participant info

Inclusion criteria

- Criteria should be narrow enough to keep the study population relatively homogenous
- But not so narrow that enrollment is unrealistic
- PI and CRC should collaborate to ensure access to subject pool

Chart review to screen for eligible subjects → "Preparatory research" falls under HIPAA Act of 1996

Image from https://fisher.osu.edu/blogs/leadreadtoday/blog/why-should-leaders-care-about-diversity-and-inclusion/

Timeline

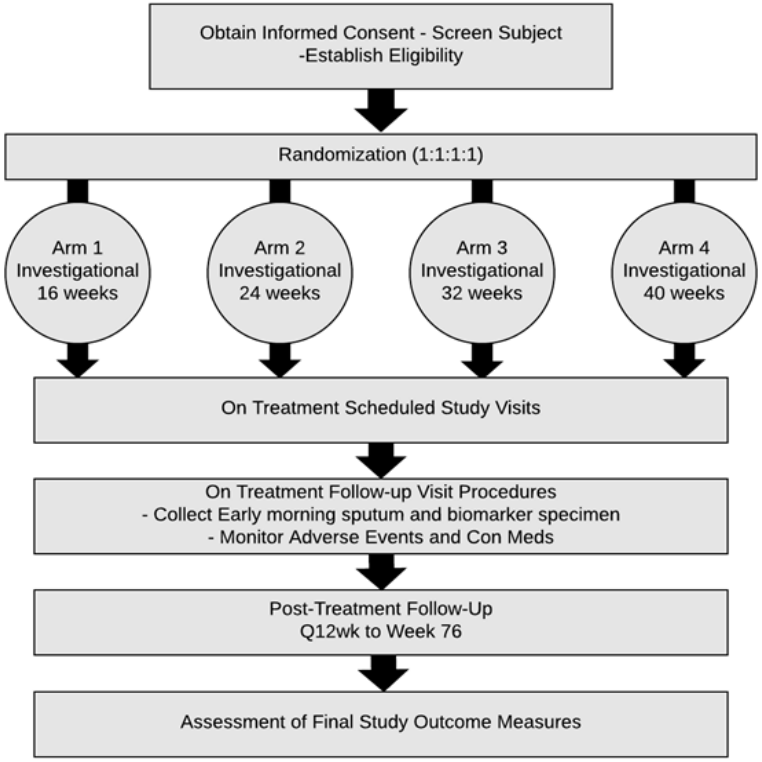
A clear and concise timeline:

- Can help guide trial conduct
- Enable external review of participant burden and feasibility
- It outlines the patient's experience at each study visit
- Can be used as a quick reference during patient visits as a checklist

Key information:

- Timing of each visit, starting from initial eligibility screening to study close-out
- Time periods of administration of trial intervention
- List of assessments performed on participants at each visit
- Any exceptions to the assessments

Timeline


Obtain Informed Consent - Screen Subject
-Establish Eligibility
Randomization (1:1:1:1)
Arm 1
Investigational
16 weeks
Arm 2
Investigational
24 weeks
Arm 3
Investigational
32 weeks
Arm 4
Investigational
40 weeks
On Treatment Scheduled Study Visits
On Treatment Follow-up Visit Procedures
- Collect Early morning sputum and biomarker specimen
- Monitor Adverse Events and Con Meds
Post-Treatment Follow-Up
Q12wk to Week 76
Assessment of Final Study Outcome Measures

Timeline

Treatment periods	Pre-treatment		Treatment visits (Wk 2, wk 4, and every 4 weeks after until treatment completion)										Post treatment follow up (every 12 wks until wk 76)			Final Visit			
Visit	1 Screening	2 Baseline	2a	3	3a	4	4a	4b	4c	5	6	7	8	9	10	11	12	13	14
Day/Week/Month	Day		Weeks																
	14 to -1	0	1[9]	2	3[9]	4	5[9]	6[9]	7[9]	8	12	16	20	24	28	32	36	40	44
Consent	X																		
Medical History[1]	X			X		X				X	X	X	X	X	X	X	X	X	X
Fundoscopic Exam[2]	X			X		X				X									
Physical Exam	X			X		X				X	X	X							
Neurologic Exam[2]	X			X		X				X									
HIV	X																		
HCV, HBV		X																	
CXR[3]	X																		
12 Lead ECG & QTcF[4]	X	X[8]	X[9]	X	X[9]	X	X[9]	X[9]	X[9]	X	X	X							
CBC[5]	X	X		X		X				X	X	X							
Serum HCG[5]	X			X		X				X	X	X							
Urine HCG[5]		X																	
Blood Chemistry[4]	X	X		X		X				X	X	X							

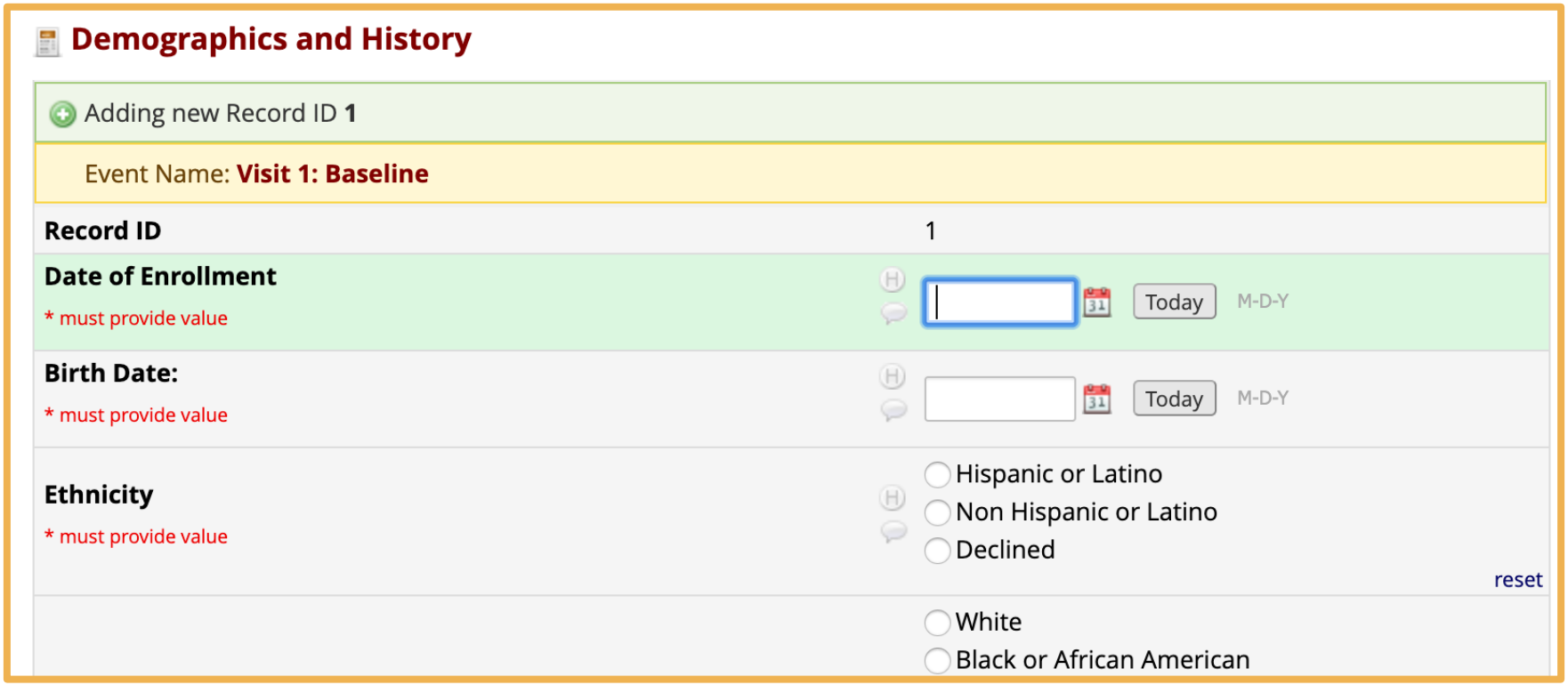
[1] Includes concomitant medications;
[3] To be performed only if one is not available from within 2 months from screening
[4] Until 4 weeks after last treatment visit.
[5] Women of childbearing age.

Data collection and management

Excellent for prospective studies:

- Surveys
- Subject data entry
- Longitudinal studies

REDCap
Research Electronic Data Capture



Data collection and management

Excellent for prospective studies:

- Surveys
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- Longitudinal studies

REDCap
Research Electronic Data Capture

NEW Record ID **1**

Data Collection Instrument	Visit 1: Baseline	Visit 2: 3 Months	Visit 3: 6 Months	Visit 4: 9 Months	Visit 5: 12 Months
Demographics and History	○				
9-5-2-1-0 Screener	○	○	○	○	
Physical Exam	○	○	○	○	○
Complete Blood Draw	○		○		○
Imaging	○				○

For a retrospective study, Excel is acceptable

Outcomes

Primary outcome	Secondary outcomes
What do these data directly tell you that answers your question?	What else can you figure out now that you have these data?

Example

Question: How long do children wash their hands when asked to do so at the end of a regularly scheduled well-check appointment?

Primary	Secondary
Hand washing information	Age Race Ethnicity History of bacterial infections History of viral infections

Data monitoring

- Periodic inspection of the outcome data by study group is necessary for some trials.
- A trial should be modified or discontinued when the accumulated data have sufficiently disturbed the clinical equipoise that justified the trial.
- Certain trials warrant some form of data monitoring. Trials with a short duration or known minimal risks do not need a formal committee.

Data Monitoring Committee (DMC)

- Consists of members from a variety of disciplines
- To periodically review the data and determine if a trial should be modified or discontinued.
- Independent from sponsor and trial investigators "completely uninvolved in the running of the trial and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial."

Data monitoring

- The protocol should name the chair and members of the DMC.
- If unknown, indicate intended size and characteristics, roles and responsibilities, planned method of functioning.
- A charter is recommended for detailing this information.

Interim analyses

- To formally monitor the accumulating data in clinical trials.
- They are generally performed in trials that have a DMC, longer duration of recruitment, and potentially serious outcomes.

The results of these analyses, along with non-statistical criteria, can be part of a stopping guideline that helps inform whether the trial should be continued, modified, or halted earlier than intended for benefit, harm, or futility.

Harms

Evaluation of harms enables monitoring of participants and appropriate management of adverse events

What to include in the protocol?

- Frequency of data collection, overall surveillance and instruments to be used.
- Distinguish between anticipated vs unanticipated, and solicited vs unsolicited.
- The reporting of harms to relevant regulatory groups, funders, and IRBs
- For multi-center studies, procedures and timings for central collection, evaluation, and reporting of pooled data
- How long after intervention are AEs being collected for?
- Definitions of SAEs, including conditions for discontinuation and the follow up required.

Relevant concomitant care

Comparable study groups should only differ by the intervention being evaluated, so any outcome differences can be attributed to effects of the intervention.

For comparability of study groups, protocol should list relevant concomitant care and interventions that are allowed, and those that are prohibited.

Be specific and include any lengths of times that the concomitant care is allowed for

Examples:

1. Rescue medication
2. In a multi-drug resistant TB trial, the background regimen

Writing Informed Consent

Main topics to get across:

- Voluntary
- Does not affect quality of care
- Risks/benefits

Understandable language for low health literacy and possibly in multiple languages.

Logistics:

- WHO will be obtaining consent
- WHERE it will be done
- HOW patients will be found (recruitment)

All this goes into the consent process and belongs in your protocol

Explaining Informed Consent

GUIDELINES FOR OBTAINING INFORMED CONSENT:

1. Always be sensitive and polite.

- Address the patient directly. "If *you* choose to participate, *you* would get an ultrasound of *your* liver, so we'll put a probe here on *your* body and press a button to measure…"
- If the caregiver asks a question, use appropriate pronouns. If preferred pronouns are not listed in the patient's chart, use they/their.
- If they say no, it is 100% okay. They can contact us later if they change their mind.

2. Be comfortable with the basic purpose of this study.

3. Know the logistical details of what the participant would be asked to do.

- Short survey at the start of each of their follow up appointments
- Parking at CTRB in the study participant spots → check in at desk for Dayton study
- Parking for MBI in north tower visitor lot → enter MBI main doors
- Payment for participation in form of Visa gift card
- Fibroscan takes ~30 mins and MRI takes ~1hr (at most)

Explaining Informed Consent

Overview of Consent Process	Example
Enter the room	*knock knock*
Introduce yourself	"My name is XXX and I am working with Dr. XXX on a study related to the health of transgender youth…"
Study aims in a couple simple sentences	"We are interested in how a person's liver and metabolism might be affected by XXX treatment…"
What the patient would do as a participant	"If you choose to participate, you would get an ultrasound of your liver, so we'll place a little probe here on your body and press a button to measure…"
Risks and benefits	"You might feel claustrophobic in the MRI, and it makes a loud noise. There are no direct benefits to you. You will be compensated for your participation…"
Say these sentences →	"This is completely voluntary and you can withdraw at any time. Saying yes or no will not affect your healthcare in any way."
Answer questions	"Do you have any questions?"
Assess interest	"Are you interested in participating?"
Consent and assent	"Since you are a minor, I need a signature from mom and you'll just say out loud that you agree to participate."
Give the patient a copy of the ICF	"Here's a copy of the consent form with our contact information."
Leave the room	"Thank you!"
Complete the consent checklist and file with ICF	

Explaining Informed Consent

To explain informed consent, you must understand:

- the protocol
- the investigator's priorities
- the subject's priorities
- potential compliance issues
- the subject's rights

		Yes	No	Date	Staff Initials
1	Discussed study with potential subject and caregiver.	☐	☐		
2	Copy of ICF given to subject and time for review and discussion was provided.	☐	☐		
3	The subject met all eligibility requirements	☐	☐		
4	The subject's verbal assent is documented on ICF.	☐	☐		
5	The caregiver signed and dated the ICF, and listed relationship to subject.	☐	☐		
6	Caregiver provided consent for subject to participate.	☐	☐		
7	Subject provided verbal assent to participate.	☐	☐		
8	ICF was signed and dated by IRB-approved research personnel	☐	☐		
9	Did the subject, parent/LAR, and study staff enter the same date on the ICF?	☐	☐		
10	ICF free of strikeouts or changes.	☐	☐		
11	Subject consented with valid, IRB-01 approved version of the ICF.	☐	☐		
12	Consent was obtained before initiation of study procedures or data collection.	☐	☐		
13	Original signed ICF on file	☐	☐		
14	Copy of ICF given to subject/family.	☐	☐		

Matching?

7 minutes

Activity 3: Match the sentence or phrase to the section of the protocol where it comes from

a) Patients will be advised that participation is completely voluntary and will not affect routine care.

b) Power analysis indicates an ideal study population of 40 trial and 40 control participants.

c) Results of this study will also inform on the average age and demographics of patients attending well-check visits.

d) The purpose of the study is to understand the sensitivity and specificity of procalcitonin levels as a measure of bacteremia.

e) However, the incidence rate of cardiac arrest in geriatric heart transplant patients across the state is yet unknown.

f) Individuals age 18-24 actively enrolled in an undergraduate institution will be eligible to participate.

g) There is a chance of fall injury while performing gait assessments.

h) While on the study, participants will receive monthly EKGs to monitor for drug-induced tachycardia.

Matching?

3 minutes

Answer

Consent	a)	Patients will be advised that participation is completely voluntary and will not affect routine care.
Sample size	b)	Power analysis indicates an ideal study population of 40 trial and 40 control participants.
2° outcomes	c)	Results of this study will also inform on the average age and demographics of patients attending well-check visits.
Objective	d)	The purpose of the study is to understand the sensitivity and specificity of procalcitonin levels as a measure of bacteremia.
Background	e)	However, the incidence rate of cardiac arrest in geriatric heart transplant patients across the state is yet unknown.
Inclusion criteria	f)	Individuals age 18-24 actively enrolled in an undergraduate institution will be eligible to participate.
Risks	g)	There is a chance of fall injury while performing gait assessments.
Timeline	h)	While on the study, participants will receive monthly EKGs to monitor for drug-induced tachycardia.

Wrap up

A research protocol is a document that describes the…

- *Background*
- *Rationale*
- *Objectives*
- *Design*
- *Methodology*
- *Statistical considerations*
- *And organization*

…of a clinical research project.

Resources

UF IRB-01 (Clinical):
http://irb.ufl.edu/irb01/irb-01.html

UF IRB-02 (Behavioral):
http://irb.ufl.edu/irb02.html

UF Biostatistics Research Design Program:
https://www.ctsi.ufl.edu/about/ctsi-programs/research-design-and-analysis/

Integrated Data Repository:
https://idr.ufhealth.org/services/analyst-data-support-services/idr-data-request-form/

NIH Protocol e-template:
https://www.centerwatch.com/articles/24509-nih-online-tool-strengthens-protocol-collaboration

SPIRIT checklist :
Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ [Internet]. 2013 Jan 9 [cited 2020 Jan 14];346. Available from: https://www.bmj.com/content/346/bmj.e7586

UVM Local IRB resources:
https://www.uvm.edu/rpo/uvmclick-irb-forms-library

UVM Commons Site – OCTR Intranet resources:
https://commons.med.uvm.edu/dean/comclntril/SitePages/Regulatory%20Documents%20and%20Resources.aspx

UVM Biomedical Statistics Research Core:
https://www.uvm.edu/biostatistics

BUMC Local IRB resources:
http://www.bumc.bu.edu/irb/inspir-ii/irb-templates/

BU CRRO:
http://www.bumc.bu.edu/crro/research-and-regulatory-consultations/

BU library resources:
http://www.bumc.bu.edu/medlib/services/research-help/

Questions?

UFHealth Shands children's Hospital

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